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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 07/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/691,412	KRANIAS ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *1-14,16,17 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15, 18, 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Newly submitted claim 20 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claim 20 is directed to a protein sequence. Had it been present in the claims as originally filed, it would have been designated in group III, drawn to a phospholamban polypeptide classified in class 530, 350.

The inventions of groups I and III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the invention of group III is not used in the invention of group I. Further, the different inventions have different designs, modes of operation and effects.

The inventions of groups II and III are patentably distinct because they are drawn to different products having different structures and functions. The nucleic acid of group II is composed of deoxyribonucleotides linked by phosphodiester bonds and assumes the form of a double helix. The polypeptide of group III is composed of amino acids linked by peptide bonds and can assume complex tertiary structures. The products of groups II and III can be used in materially different processes, for example the DNA of group II can be used in hybridization assays, and the polypeptide of group III can be used to make a fusion protein with an enzymatic function. Consequently, the reagents, reaction conditions, and reaction parameters required to make or use each invention are different. Therefore, the inventions of groups II and III are patentably distinct from each other. The search for each of groups II-III presents a serious search burden as the searches for each are not coextensive in scope. The inventions have different

status in the art as shown by their different classifications. In cases such as this one where descriptive sequence information is provided, the sequences are searched in appropriate databases. There is search burden also in the non-patent literature. Prior to the concomitant isolation and expression of the sequence of interest there may be journal articles devoted solely to polypeptides which would not have described the polynucleotide. Similarly, there may have been "classical" genetics papers which had no knowledge of the polypeptide but spoke to the gene. Searching, therefore is not coextensive.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 20 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

2. Currently, claims 1-17 and newly added claims 18-20 are pending in the instant application. Claims 1-14, 16, 17, and 20 are withdrawn from consideration as being drawn to non elected inventions and claims 18-19 are newly added. Claims 15, 18, and 19 are currently under examination. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are newly applied as necessitated by amendment. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

3. The amendment to the specification filed 4/25/2006 has been entered. The objection to the specification made in the previous office action is moot in view of the amendment.

4. The substitute sequence listing filed 4/25/2006 has been entered.

Claim Rejections - 35 USC § 112

5. Claims 15 and newly added claims 18 and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Amended claim 15 appears to encompass any nucleic acid comprising SEQ ID NO: 7, but which is polymorphic at any position with respect to SEQ ID NO: 7 or polymorphic on either side of SEQ ID NO: 7, as well as any fragments of such polymorphic SEQ ID NO: 7 (it is noted that the interpretation of newly amended claim 15 in the response at page 3 clearly continues to encompass fragments) from any source. The claims therefore encompass an extremely large genus of nucleic acid variants, homologs, and mutants of SEQ ID NO: 7, from any source. The specification, however, has only described a single polymorphism within SEQ ID NO: 1, T to G at position 116, which is associated with dilated cardiomyopathy (DCM) when present as a homozygous mutation (see pages 10-11 and 16 of the specification; now SEQ ID NO: 7). SEQ ID NO: 7 appears to encode the full length 52 amino acid human phospholamban protein with a mutation at position 116 which replaces the T in SEQ ID NO: 1 to a G. The claimed recitation,

however, encompasses a large genus of nucleic acids which comprise polymorphisms at any position of SEQ ID NO: 7 or anywhere in genomic sequences on either side of SEQ ID NO: 7. The genus includes an enormous number of polymorphisms for which no written description is provided in the specification.

Newly added claims 18 and 19 encompass any mutant, variant or homolog phospholamban nucleic acid *from any source* which comprises a mutation that results in deletion of a cleavage site for a restriction endonuclease as well as any mutation which results in an L39X mutation in any phospholamban sequence. The newly added claims encompass an enormous genus of nucleic acids for which only a single sequence has been described. The specification provides no description of any other mutations which result in deletion of a cleavage site in humans, nor any such polymorphisms in any other species. Other than providing the sequence of SEQ ID NO: 1 and defining the T to G mutation at position 116, the specification does not describe the attributes needed for a nucleic acid to be generally identified as "a phospholamban polymorphism". With regard to claim 19, the only mutation in humans supported by the specification is a T to G mutation at position 116 of SEQ ID NO: 1, and the only other mutation described is in the rabbit phospholamban protein which results in a L39X mutation. However, without a reference for the number "39", it is not clear what position "39" the claim refers to. The claim broadly encompasses any nucleic acid which would encode a stop codon at position "39" of any phospholamban mutant, variant, or homolog sequence from any source.

This large genus is represented in the specification by only the particularly named polymorphism for which data is provided demonstrating an association in homozygous form with DCM. Thus, applicant has express possession of only 1 particular polymorphism, in a

genus which comprises hundreds of millions of different possibilities. Here, no common element or attributes of the sequences are disclosed which would permit selection of sequences as polymorphisms. No written description of alleles, of upstream or downstream regions containing additional sequence, which are mutated or associated with DCM are described in the specification. The single T to C polymorphism at position 116 within SEQ ID NO: 1 is not representative of the large genus of mutants and variants of SEQ ID NO: 7 or homologs of SEQ ID NO: 7 from any source. For example, Schmitt (Schmitt et al; Science, vol. 299, pages 1410-1413; 2003) teaches a C to T mutation at position 25 leading to an Arg to Cys mutation at amino acid 9, of human phospholamban. The instant specification provides no description or guidance as to the existence of this polymorphism. The instantly disclosed polymorphism leading to a stop codon at amino acid 39 does not appear to be representative of the polymorphism at position 9 taught by Schmitt because the polymorphism taught by Schmitt appears to be disease associated in the heterozygous state whereas the instantly disclosed polymorphism at position 116 only appears associated in the homozygous state (specification at page 16 teaches that individuals in the heterozygous state did not show any detectable clinical phenotype). Secondly, the instantly disclosed polymorphism results in a mutation in the transmembrane domain of phospholamban, whereas the mutation disclosed by Schmitt is in domain Ia. The teachings of the specification provide no way to predict the existence or affect of the polymorphism taught by Schmitt.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of

skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) In the instant case, the specification fails to teach the necessary common attributes or features of the genus of encompassed nucleic acids and polymorphisms in view of the species disclosed. As such, one of skill in the art would not recognize that applicant was in possession of the genus of nucleic acids and polymorphisms encompassed by the broadly claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acids and polymorphisms, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The current situation is a definition of the compound solely based on its functional utility, as a polymorphism, without any definition of the particular polymorphisms claimed.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

Response to Arguments

6. The response traverses the rejection and states that "as the examiner noted, the present disclosure fully supports the subject matter of claim 15". This argument has been thoroughly reviewed but was not found persuasive as the previous office action did not indicate that a claim as presently recited for claim 15, would meet the provisions of the written description requirement of 35 USC 112/first paragraph. The previous office action noted that the only polymorphism taught in the specification was a T to G mutation at position 116 of SEQ ID NO: 1. It is clear from the interpretation of the claim with regard to the term "polymorphism" made in the previous office action and reiterated above, as well as the rejection made under 35 USC 112/second paragraph, that such encompasses "a large genus of nucleic acids which comprise polymorphisms at any position of SEQ ID NO: [1] 7 or anywhere in genomic sequences on either side of SEQ ID NO: [1] 7.". The deletion of the term "fragment" and the change in designation of SEQ ID NO: 7 instead of SEQ ID NO: 1 does not remedy this. The claims as

recited continue to encompass polymorphisms within the recited sequence as well as on either side. This rejection can be overcome for claim 15 by reciting instead "an isolated nucleic acid molecule comprising SEQ ID NO: 7".

7. Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim recites "an isolated phospholamban polymorphism *comprising* SEQ ID NO: 7". This recitation is confusing because the term "comprising" is normally taken to mean the full sequence of SEQ ID NO: 7 with any nucleotides on either side. However, the use of the term "polymorphism" in the context is unclear in this situation because it appears to encompass any polymorphism of SEQ ID NO: 7. However, the only mutation/polymorphism taught in the specification is at position 116 of SEQ ID NO: 1, wherein said position is a G instead of a T. It is not clear if the claim is intended to be drawn to "an isolated nucleic acid molecule comprising SEQ ID NO: 7" or to any nucleic acid which is polymorphic to SEQ ID NO: 7. Additionally, the interpretation of the claim with regard to the removal of "fragment", made at page 3 of the response is not clear. The response states "'Fragment'" has been deleted from the claim since it is understood that a fragment of a nucleic acid comprising the inventive polymorphism is included within the scope of the claim". Accordingly, the use of the term "comprising" remains confusing because it does not appear to be limited to the sequence of SEQ ID NO: 7, which is contrary to the usual use of the transitional term. Accordingly, it is not clear whether the term "comprising" is limited to the sequence of SEQ ID NO: 7 with any nucleotides on either side, to

any sequence which is polymorphic to SEQ ID NO: 7 (that is, any mutation/polymorphism within or outside of SEQ ID NO: 7), or to any sequence which is smaller than such. The metes and bounds of the claim are therefore unclear.

Claim 19 is indefinite in the recitation of "L39StopCodon" as the number used has no reference. In other words, the number is arbitrary without a reference with which to compare it to. In the instant case, the claim broadly reads on any phospholamban sequences from any species, including mutants, variants, and homologs, such that it is unclear what position the number "39" refers to. For example, does the term refer to any 39th nucleic acid in a sequence or any 39th codon so long as it is the 39th codon in a sequence, or to a nucleotide or codon position which could be the 39th codon in a sequence (but is not due to a truncation for example). The metes and bounds of the claim are therefore unclear.

Claim Rejections - 35 USC § 102

8. Claims 15 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Genbank Accession number X15075 (September 1993) as evidenced by New England Biolabs, 1995 catalog, page 13.

Accession number X15075 teaches the mRNA for pig phospholamban which is polymorphic with respect to SEQ ID NO: 1 at 10 positions (10 mismatches -see alignment). Given that neither the claim nor the specification provides any definition of "comprising" or polymorphism (see 112/2nd paragraph rejection above), the claim has been broadly interpreted to encompass a nucleic acid that has polymorphisms or mutations with respect to SEQ ID NO: 7. With regard to claim 18, the recitation of "comprising a mutation that results in deletion of a

cleavage site for restriction endonuclease" has been given no patentable weight as the method of obtaining the nucleic acid, that is mutating it, does not distinguish from a nucleic acid itself. A nucleic acid molecule is defined by its sequence, not by the fact that it was obtained by mutation. Accordingly, Accession number X15075 contains a number of sequences which could comprise a cleavage site for a restriction enzyme but do not. For example, X15075 comprises the sequence of "ACCT" (positions: 253-256), which is not recognized by AluI, which normally cleaves at "AG/CT". Thus the recitation of "comprising a mutation that results in deletion of a cleavage site for a restriction endonuclease" does not distinguish the claimed molecule from that of Accession number X15075. [It is noted that the sequence of X15075 is specifically polymorphic at the position which corresponds to position 81 of SEQ ID NO: 1 or 7 (see alignment). The human sequence comprises the polynucleotide AGCT, whereas the sequence of X15075 comprises "ACCT"].

9. Claims 15 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Genbank Accession number M60411 (Jan 1995).

With regard to claim 15, the recitation of "polymorphism comprising..." has been broadly interpreted to encompass a nucleic acid molecule which is polymorphic with regard to SEQ ID NO: 7. Accession number M60411 teaches the mRNA for human phospholamban which comprises SEQ ID NO: 1 and is polymorphic with regard to SEQ ID NO: 7. With regard to claim 18, the recitation of "comprising a mutation that results in deletion of a cleavage site for restriction endonuclease" has been given no patentable weight as the method of constructing the nucleic acid, that is mutating it, does not distinguish from a nucleic acid itself. A nucleic acid

molecule is defined by its sequence, not by the fact that it was obtained by mutation. Accordingly, Accession number M60411 contains a number of sequences which could comprise a cleavage site for a restriction enzyme but do not. Thus the recitation of "comprising a mutation that results in deletion of a cleavage site for a restriction endonuclease" does not distinguish the claimed molecule from that of Accession number M60411.

10. Claims 15 and 18 are rejected under 35 U.S.C. 102(a) as being anticipated by Kimura (Kimura et al; Mol. Pharmacol, vol. 61, pages 667-673, 2002).

Kimura teaches constructing S16D and T17D mutants of human phospholamban DNA (see col. 2, page 668 "Oligonucleotide directed mutagenesis) from a fragment of the DNA encoding human phospholamban: Met-1 to Gln-26. The claim has been broadly interpreted to encompass a nucleic acid which is a fragment of SEQ ID NO: 7 and which has polymorphisms with respect to SEQ ID NO: 7. As noted in the response, the deletion of the term "fragment" has not removed the limitation from what is encompassed by the claim (see response page 3, lines 82-84). With regard to claim 18, the recitation of "comprising a mutation that results in deletion of a cleavage site for restriction endonuclease" has been given no patentable weight as the method of constructing the nucleic acid, that is mutating it, does not distinguish from a nucleic acid itself. A nucleic acid molecule is defined by its sequence, not by the fact that it was obtained by mutation. Accordingly, Kimura teaches nucleic acid molecules which could comprise a cleavage site for a restriction enzyme but do not. Thus the recitation of "comprising a mutation that results in deletion of a cleavage site for a restriction endonuclease" does not distinguish the claimed molecule from those taught by Kimura.

11. Claims 15, 18, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Brennan (US Patent 5,474,796).

As noted in the response at page 3, claim 15 appears to encompass fragments of the recited SEQ ID NO:, which has no defined length. Claims 18 and 19 specifically encompass fragments with no defined length. Brennan teaches every permutation of trimer nucleic acid molecules, as well as specifically "TGA" (see Figure 1A) which encodes a stop codon (claim 19). Further, Brennan teaches making every possible 10 mer nucleic acid. Accordingly, the teachings of Brennan anticipate the broad genus of nucleic acids encompassed by the claims.

Response to Arguments

The response traverses the rejections under 35 USC 102 of claim 15 and states that none of the references teach the polymorphism comprising SEQ ID NO: 7. This argument has been thoroughly reviewed but was not found persuasive as the term "comprising" in the context of "polymorphism" does not appear limited to "a nucleic acid molecule comprising SEQ ID NO: 7" for the reasons made of record above. Accordingly, the term "polymorphism" is confusing as it appears that the claim intends to encompass sequences which are polymorphic with regard to the recited SEQ ID NO:.

Conclusion

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Jehanne Sitton
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Art Unit 1634
6/30/06